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# Alendronate and Other Bisphosphonates in Postmenopausal Osteoporosis: A Structured Narrative Critical Review of Antifracture Efficacy, Long-Term Safety, and Contemporary Treatment Sequencing

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**Abstract**

Postmenopausal osteoporosis is a chronic skeletal disorder characterized by impaired bone strength and an increased risk of fragility fractures. Bisphosphonates have remained a central component of pharmacological management for more than three decades because of their established ability to reduce vertebral and, in appropriately selected populations, nonvertebral and hip fracture risk. Among oral bisphosphonates, alendronate has one of the most extensive evidence bases, encompassing landmark randomized controlled trials, long-term extension studies, and subsequent systematic reviews. This structured narrative review critically examines the clinical evidence for bisphosphonate therapy, with particular emphasis on alendronate. Evidence from pivotal randomized trials, long-term extension studies, systematic reviews, and contemporary guidelines is evaluated with regard to fracture-specific outcomes, absolute treatment benefit, long-term safety, and treatment duration. Alendronate consistently reduces vertebral fracture risk, whereas its effects on nonvertebral and hip fractures require interpretation in relation to baseline fracture probability and the certainty of available evidence. Current evidence favors a risk-stratified approach in which bisphosphonates remain appropriate initial therapy for many women at high fracture risk, while selected patients at very high or imminent risk may benefit from an osteoanabolic-first strategy followed by antiresorptive treatment. The contemporary value of alendronate therefore depends on appropriate patient selection, treatment sequencing, and periodic reassessment of the individual benefit–risk balance.

**Keywords:** postmenopausal osteoporosis; bisphosphonates; alendronate; fracture

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## 1. Introduction and Therapeutic Rationale

Osteoporosis is a chronic skeletal disease characterized by compromised bone strength and increased susceptibility to fragility fractures. Its clinical consequences extend substantially beyond reduced bone mineral density (BMD), because osteoporotic fractures are associated with pain, loss of mobility, functional decline, disability and reduced quality of life. Hip fractures are additionally associated with substantial excess mortality, particularly in older adults [1–4]. The principal objective of osteoporosis treatment is therefore not

simply to increase BMD, but to reduce the probability of clinically relevant fractures. This distinction is fundamental because BMD is an important determinant of fracture risk but does not completely describe skeletal fragility. Age, previous fracture, fracture site, glucocorticoid exposure, falls, frailty and other clinical characteristics contribute independently to overall fracture probability [5,6]. The postmenopausal period is associated with accelerated bone loss related predominantly to estrogen deficiency. Nevertheless, fracture risk is heterogeneous among postmenopausal women. A woman with a T-score of −2.6 without previous fracture and relatively few additional risk factors may have a substantially different absolute fracture probability from a woman of the same BMD who recently sustained a vertebral or hip fracture. This heterogeneity has important implications for treatment selection. Current guidelines [7–9], together with a contemporary clinical review [10], support bisphosphonates for many women at high fracture risk while recognizing that selected patients at very high or imminent risk may benefit from another initial treatment strategy. Bisphosphonates represented a major therapeutic advance because they inhibit osteoclast-mediated bone resorption and, unlike many other antiresorptive agents, become incorporated into the skeleton. Their prolonged skeletal retention provides persistent biological activity after treatment cessation and contributes to their distinctive long-term therapeutic profile [11–13]. Alendronate was among the first bisphosphonates to establish convincing evidence for fracture prevention in postmenopausal osteoporosis. Its clinical development included randomized placebo-controlled trials in women with established vertebral fractures and in women with low BMD without baseline vertebral fractures [14–17]. These trials became foundational evidence for the use of alendronate and, more broadly, for bisphosphonate therapy in osteoporosis. However, the accumulated evidence does not justify an uncritical conclusion that all patients with osteoporosis should receive bisphosphonates indefinitely.

The contemporary clinical question is more complex:

> Which patient should receive a bisphosphonate, which bisphosphonate should be selected, for how long, and what should happen when the patient's fracture risk changes?

This question is particularly relevant because the therapeutic landscape has evolved considerably. Osteoanabolic agents and newer antiresorptive therapies have expanded treatment options, while increasing recognition of rare complications and suboptimal long-term adherence has challenged the concept of prolonged treatment without reassessment [10,18–21].

The 2024 position statement of the American Society for Bone and Mineral Research (ASBMR) and the Bone Health and Osteoporosis Foundation (BHOF) reflects an important shift toward goal-directed osteoporosis treatment, in which therapeutic decisions are guided by fracture history, the recency and severity of fractures, and the patient's overall fracture probability rather than BMD alone [10]. The updated UK guidance adopts a similarly individualized approach, while continuing to recommend oral alendronate and risedronate, as well as intravenous zoledronate, as established treatment options for many patients at increased fracture risk [8]. Nevertheless, these recommendations also highlight a clinically relevant dilemma: treatment with bisphosphonates may be appropriate as an initial strategy for some women, whereas others, particularly those at very high or imminent fracture risk, may achieve greater benefit from an anabolic-first approach.

Against this background, the purpose of the present review is not merely to summarize the established antifracture efficacy of bisphosphonates. Rather, it is to critically examine how evidence from pivotal clinical trials, long-term extension studies, contemporary systematic reviews, and evolving treatment guidelines should inform the selection and duration of bisphosphonate therapy. Particular attention is given to alendronate, for which extensive clinical evidence allows a detailed consideration of fracture-specific outcomes,

differences between relative and absolute treatment benefit, residual effects after discontinuation, and the implications of long-term safety and adherence. By integrating these aspects with current risk-stratified and sequential treatment strategies, this review aims to clarify the circumstances in which alendronate remains an appropriate initial treatment and those in which an alternative therapeutic sequence may be preferable. The contribution of this review is a decision-focused comparison of what different types of evidence can—and cannot—establish about alendronate. Specifically, it contrasts relative with absolute fracture benefit across Fracture Intervention Trial (FIT) populations; separates discontinuation data from evidence of sustained BMD effects; evaluates exposure-dependent rare harms against fractures prevented; and connects these findings to adherence and treatment sequencing. Compared with recent overviews of long-term and sequential osteoporosis care [22,23], the emphasis is on the limitations and clinical applicability of pivotal alendronate data rather than a comprehensive inventory of osteoporosis drugs.

## 2. Literature Search and Evidence Selection

This article is a structured narrative critical review. The evidence was organized around defined clinical themes relevant to treatment decisions: fracture-specific efficacy, absolute versus relative benefit, duration and discontinuation, adverse effects, adherence, and sequential therapy. Information sources were PubMed/MEDLINE and the Cochrane Library, supplemented by guidance from major professional societies (Endocrine Society, National Osteoporosis Guideline Group, ESCEO/IOF and ASBMR/BHOF). Searches combined terms for the population (postmenopausal osteoporosis) and interventions (bisphosphonates, alendronate, risedronate, zoledronate) with theme-specific terms (fracture, discontinuation, drug holiday, atypical femoral fracture, osteonecrosis of the jaw, adherence, persistence, sequential therapy, romosozumab, teriparatide, abaloparatide and denosumab discontinuation). The literature was last checked before submission of the revised manuscript (12 November 2026). Only publications in English were considered, and no restriction on publication date was applied so that landmark trials could be retained. Sources were selected by the authors according to the criteria below, and the final set of evidence was agreed by consensus among all authors.

Priority was given to randomized controlled trials, long-term randomized extension studies, systematic reviews and meta-analyses, and recent clinical guidelines or expert position statements directly addressing postmenopausal osteoporosis. Landmark older trials were retained when they provided pivotal efficacy or long-term evidence that has not been superseded. Studies were included when they directly informed fracture-specific efficacy, absolute treatment benefit, duration and persistence of effect, safety, adherence, or contemporary treatment sequencing. Animal or in-vitro studies, reports focused on non-osteoporosis bisphosphonate dosing, and publications without direct relevance to the clinical questions of this review were not used as core evidence. Evidence was synthesized narratively, with particular attention to absolute event rates, confidence intervals, certainty of evidence, and applicability to contemporary patients. No review protocol was prepared or registered. Instead of a formal study-level risk-of-bias assessment, certainty of evidence was taken, where available, from published Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessments, particularly the 2025 Cochrane review [24], and the design-related limitations and applicability of individual studies are discussed in Section 6. Reporting of this narrative review was guided by the SANRA (Scale for the Assessment of Narrative Review Articles) criteria [25].

## 3. Bisphosphonates and Alendronate: Pharmacological Basis and Antifracture Evidence

### 3.1. Pharmacological Basis

Bisphosphonates are synthetic analogues of pyrophosphate in which the central oxygen atom is replaced by carbon. This structural modification makes them resistant to enzymatic degradation and enables strong binding to hydroxyapatite within bone [11–13]. Nitrogen-containing bisphosphonates, including alendronate, exert their principal pharmacological effect through inhibition of farnesyl pyrophosphate synthase within the mevalonate pathway. This interferes with protein prenylation required for osteoclast function, cytoskeletal organization and survival, thereby suppressing bone resorption [11–13]. Their pharmacokinetic characteristics are clinically important. Oral bioavailability is low and is markedly affected by food and mineral-containing products. The absorbed fraction is either eliminated through the kidneys or binds to bone. During subsequent bone remodeling, bisphosphonate molecules can be released from the mineralized matrix and become available to osteoclasts [11–13]. This skeletal retention has two opposing implications. It contributes to prolonged therapeutic effects after treatment cessation, but it also raises the theoretical concern that excessive cumulative suppression of bone remodeling may contribute to rare complications associated with long-term exposure. Alendronate therefore has a distinctive pharmacological profile: it combines strong antiresorptive efficacy with prolonged skeletal retention, relatively inexpensive oral administration, and the possibility of residual protection after discontinuation.

### 3.2. Landmark Evidence for Alendronate

Early randomized trials demonstrated that alendronate increases BMD and reduces vertebral fracture risk in postmenopausal women with osteoporosis [14]. These findings were subsequently confirmed and expanded by the Fracture Intervention Trial (FIT). The vertebral-fracture arm of FIT included 2027 postmenopausal women with low femoral-neck BMD and at least one existing vertebral fracture. After approximately three years, alendronate significantly reduced the incidence of new radiographic vertebral fractures and clinical fractures compared with placebo. Reductions in hip and wrist fractures were also observed [15]. These findings provided particularly strong evidence for alendronate in women with established vertebral fragility fractures. The second major FIT trial included 4432 women with low BMD but no existing vertebral fracture [16]. The results were more nuanced. Alendronate significantly increased BMD and reduced radiographic vertebral fractures, but the overall reduction in clinical fractures did not reach statistical significance in the entire cohort. In the subgroup with baseline osteoporosis at the femoral neck, however, the reduction in clinical fracture risk was statistically significant (Table 1) [16]. This trial illustrates a central principle of osteoporosis therapeutics: relative efficacy and absolute clinical benefit are not synonymous. A treatment may produce a similar relative effect across populations while generating substantially greater absolute benefit in patients with higher baseline fracture probability. A pooled analysis of FIT further demonstrated significant reductions in vertebral, clinical and hip fractures with alendronate [17]. Importantly, the relative reductions were broadly similar in women with and without pre-existing vertebral fractures. Therefore, the evidence should not be interpreted as showing that alendronate is intrinsically more effective in women with previous vertebral fractures. Rather, patients with greater baseline fracture risk are expected to experience greater absolute benefit. The 2025 Cochrane review provides an important contemporary reassessment of this evidence. It included 119 eligible studies, with 102 contributing usable data, and evaluated alendronate separately for primary and secondary fracture prevention [24]. The review concluded that alendronate probably reduces clinical vertebral fractures in secondary prevention and

may reduce nonvertebral, hip and wrist fractures, whereas several findings in primary prevention were characterized by lower certainty. This is an important refinement of the traditional interpretation of the alendronate evidence. The overall antifracture effect is well established, but the strength and certainty of evidence are not identical for every fracture type or every clinical population.

**Table 1.** Fracture-specific efficacy of alendronate in the Fracture Intervention Trial.

| Trial/Population | Follow-up | Endpoint | Alendronate vs. Placebo | RR/HR (95% CI) | ARR | NNT (Horizon) |
|---|---|---|---|---|---|---|
| FIT-1; prevalent vertebral fracture ($n = 2027$) | ~3 years | New morphometric vertebral fracture | 8.0% vs. 15.0% | RR 0.53 (0.41–0.68) | 7.0% | ~14 (3 y) |
| FIT-1; same population | ~3 years | Clinical vertebral fracture | 2.3% vs. 5.0% | HR 0.45 (0.27–0.72) | 2.7% | ~37 (3 y) |
| FIT-1; same population | ~3 years | Any clinical fracture | 13.6% vs. 18.2% | HR 0.72 (0.58–0.90) | 4.6% | ~22 (3 y) |
| FIT-2; no prevalent vertebral fracture ($n = 4432$) | Mean 4.2 years | Radiographic vertebral fracture | 2.1% vs. 3.8% | RR 0.56 (0.39–0.80) | 1.7% | ~60 (4.2 y) |
| FIT-2; same population | Mean 4.2 years | Any clinical fracture | 12.3% vs. 14.1% | HR 0.86 (0.73–1.01) | 1.8% | Not significant |
| FIT-2; femoral-neck osteoporosis subgroup | Mean 4.2 years | Any clinical fracture | Arm rates not reported here | HR 0.64 (0.50–0.82) | ~6.5% | ~15 (4.2 y) |

ARR, absolute risk reduction (placebo minus alendronate); CI, confidence interval; HR, hazard ratio; NNT, number needed to treat; RR, relative risk. Approximate NNT values are calculated as 1/ARR and refer to the stated follow-up period. FIT-1 and FIT-2 figures derive from [15] and [16], respectively. The FIT-2 subgroup arm-specific rates are not reproduced because they were not independently verified for this table.

The principal outcome-specific FIT estimates, absolute risk reductions and numbers needed to treat are summarized in Table 1. The corresponding time horizons differ: approximately three years for the vertebral-fracture arm (FIT-1) and a mean of 4.2 years for the clinical-fracture arm (FIT-2) [15,16].

### 3.3. Vertebral, Nonvertebral and Hip Fracture Outcomes

Alendronate consistently reduces morphometric vertebral fractures, but clinical vertebral, nonvertebral and hip fracture outcomes differ in event frequency, precision and clinical importance (Table 1). FIT-1 provides particularly compelling evidence in women with prevalent vertebral fractures, while FIT-2 illustrates that a reduction in radiographic fractures does not necessarily translate into a statistically significant reduction in overall clinical fractures. Within FIT-2, the subgroup with femoral-neck osteoporosis had a clinically important absolute benefit [15,16]. The 2025 Cochrane review likewise indicates that certainty varies by outcome and prevention setting [24]. Direct head-to-head fracture-outcome comparisons among bisphosphonates are limited; a 2022 network meta-analysis offers useful indirect comparisons but should not be interpreted as definitive evidence of superiority [26]. Original zoledronate trials provide complementary evidence [27,28].

### 3.4. Other Bisphosphonates and Route of Administration

Risedronate and intravenous zoledronate are established alternatives to oral alendronate for patients at increased fracture risk [8,26]. Evidence for zoledronate includes the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORI-

ZON) pivotal fracture trial in postmenopausal osteoporosis and a separate trial after hip fracture [27,28]. Once-yearly intravenous zoledronate may be particularly useful when gastrointestinal intolerance, administration difficulties, or poor adherence limits oral therapy, provided renal function and calcium/vitamin D status permit treatment [8]. Network meta-analyses support antifracture efficacy across agents, but indirect estimates do not establish definitive head-to-head superiority [26].

## 4. Long-Term Treatment, Treatment Persistence and the Bisphosphonate Holiday

The optimal duration of bisphosphonate therapy remains one of the most debated issues in osteoporosis management.

Unlike drugs whose biological effects disappear rapidly after cessation, bisphosphonates remain incorporated into bone and continue to exert antiresorptive effects during subsequent remodeling. This characteristic makes treatment discontinuation possible in selected patients but also makes the duration decision more complex.

### *4.1. Evidence for Long-Term Alendronate Therapy*

Long-term studies have demonstrated that alendronate can maintain increased BMD and suppressed bone turnover over extended periods [29]. However, evidence that treatment can be continued for up to 10 years does not mean that all women should receive uninterrupted therapy for 10 years. The most clinically informative evidence comes from the FIT Long-term Extension (FLEX) trial [30]. FLEX randomized 1099 postmenopausal women who had already received approximately five years of alendronate either to continue treatment or to discontinue it for another five years. Women who discontinued alendronate experienced moderate reductions in total-hip and lumbar-spine BMD and increases in biochemical markers of bone turnover. Nevertheless, mean BMD remained at or above levels observed approximately ten years earlier. The cumulative risk of nonvertebral fracture was essentially identical in women who continued versus discontinued therapy (19% (continuing) vs. 18.9% (discontinuing); RR 1.00, 95% CI 0.76–1.32). Continued therapy, however, reduced clinically recognized vertebral fractures (2.4% (alendronate) vs. 5.3% (placebo); RR 0.45, 95% CI 0.24–0.85), while the difference in morphometric vertebral fractures was not significant (9.8% (alendronate) vs. 11.3% (placebo); RR 0.86, 95% CI 0.60–1.22) [30]. These findings support selective continuation in women at higher vertebral-fracture risk rather than either universal continuation or universal discontinuation (Table 2).

**Table 2.** Residual effects and clinical implications of bisphosphonate discontinuation after long-term therapy.

| Evidence from Clinical Studies | Clinical Implication | Key References |
| --- | --- | --- |
| Fracture protection may persist after treatment discontinuation. | Discontinuation after approximately five years of treatment does not necessarily lead to an immediate loss of fracture protection. | [30] |
| Residual skeletal effects may persist for several years. | The anti-fracture and skeletal benefits of bisphosphonates may extend beyond the period of active treatment in many patients. | [29,30] |
| The benefits of continued therapy may differ according to baseline fracture risk. | Women at particularly high risk of clinical vertebral fracture may derive additional benefit from continuing treatment. | [30] |
| Treatment duration should therefore be individualized. | Decisions regarding continuation or discontinuation should be based on fracture risk, treatment response, and individual clinical characteristics. | [7,8,30] |

The evidence therefore supports risk-based reassessment rather than a fixed-duration approach.

### 4.2. The Concept of a Bisphosphonate Drug Holiday

A bisphosphonate holiday is a planned temporary interruption of therapy after an adequate treatment period in a patient whose current fracture risk is sufficiently low to justify withholding treatment while residual skeletal effects persist. It should not be interpreted as a universal recommendation to stop bisphosphonate therapy after five years. Current guidance generally recommends reassessment after several years of therapy. The Endocrine Society recommends reassessment after 3–5 years and consideration of a holiday in women whose fracture risk has become low to moderate [7], while the National Osteoporosis Guideline Group (NOGG) recommends at least five years of oral bisphosphonate therapy followed by reassessment, with longer treatment considered in patients with persistent high-risk characteristics [8]. These characteristics include older age, previous hip or vertebral fracture, high-dose glucocorticoid therapy and fracture occurring during treatment [8]. The critical issue is therefore not simply the elapsed treatment duration but the patient's current fracture probability.

#### 4.2.1. Patients in Whom a Holiday Is Less Appropriate

A treatment holiday is generally less appropriate in patients with:

- recent fragility fracture;
- multiple vertebral fractures;
- previous hip fracture;
- very low hip BMD;
- persistent high or very high fracture probability;
- fracture occurring despite apparently adequate treatment;
- ongoing substantial glucocorticoid exposure;
- major additional factors associated with sustained fracture risk.

For these patients, discontinuation solely because five years have elapsed may expose the patient to unnecessary fracture risk. Conversely, a patient who has completed several years of treatment, has no recent fracture, demonstrates satisfactory BMD and has a substantially reduced residual fracture probability may reasonably undergo a monitored treatment interruption.

#### 4.2.2. Monitoring During a Holiday

A treatment holiday should be regarded as an active clinical strategy rather than treatment abandonment. Clinical reassessment should include new fragility fractures, changes in major clinical risk factors and BMD where clinically appropriate. NOGG recommends reassessment after discontinuation, with approximately two years suggested for alendronate [8]. Earlier reassessment is appropriate if a new fracture occurs or if there is substantial deterioration in clinical status. Treatment should be restarted when the patient's fracture risk again becomes sufficiently high. The FLEX findings therefore support neither universal continuation nor universal discontinuation. Instead, they support individualized management according to the balance between residual fracture risk and cumulative treatment exposure.

## 5. Safety, Adherence and Contemporary Positioning of Bisphosphonates Contraindications, Precautions, and Patient Selection

Before prescribing a bisphosphonate, clinicians should assess renal function, calcium and vitamin D status, route-specific suitability, and relevant comorbidity. Pre-existing hypocalcaemia and hypersensitivity are contraindications; oral agents must not be used when oesophageal emptying is impaired (e.g., achalasia or stricture) or when a patient can-

not remain upright for the required interval. Renal thresholds are drug-specific: zoledronate is contraindicated at Glomerular Filtration Rate (GFR) ≤ 35 mL/min and risedronate at GFR ≤ 30 mL/min; alendronate is generally not recommended or requires particular caution at GFR ≤ 35 mL/min [8]. These thresholds should not be interpreted as identical regulatory wording for every agent. Untreated hypocalcaemia should be corrected before treatment. Hypercalcaemia is not a usual contraindication to osteoporosis-dose bisphosphonates; indeed, intravenous bisphosphonates are used to treat hypercalcaemia in other settings. Relevant gastrointestinal disease, tolerance of fasting administration, dental status and potential for adherence should also inform agent selection. Renal impairment and inability to comply with oral administration may favor another therapeutic approach rather than being labeled nonspecific 'bisphosphonate intolerance'.

Regarding common adverse effects in clinical practice upper gastrointestinal symptoms, including reflux, dyspepsia and oesophageal irritation, are important tolerability concerns with oral alendronate and may contribute to treatment interruption. Proper fasting administration with water and remaining upright reduce avoidable oesophageal exposure; persistent symptoms warrant reassessment of treatment suitability [8]. Intravenous zoledronate avoids these oral administration requirements but can cause a transient acute-phase reaction (fever, myalgia and influenza-like symptoms), most often after the first infusion [8,27]. Hypocalcaemia is a contraindication until corrected, and calcium/vitamin D status should be assessed before treatment, especially with intravenous therapy [8]. In the HORIZON pivotal fracture trial, serious atrial fibrillation was reported more often with zoledronate than placebo (1.3% vs. 0.5%); this safety signal was not consistently reproduced in the separate post-hip-fracture trial and does not establish causality [27].

### 5.1. Atypical Femoral Fractures

Atypical femoral fractures (AFFs) are uncommon subtrochanteric or diaphyseal fractures with characteristic radiographic features [31]. In a large observational cohort of 196,129 women, adjusted AFF risk rose with duration of bisphosphonate exposure: compared with less than three months' use, the hazard ratio was 8.86 (95% CI 2.79–28.20) after 3 to <5 years and 43.51 (95% CI 13.70–138.15) after ≥8 years [32]. These are relative estimates against a very short exposure category and should not be confused with absolute fracture probability. Absolute risk remained low and declined promptly after discontinuation. In the same study's three-year benefit–harm model, among 10,000 White women treated, approximately 149 hip fractures were prevented for two bisphosphonate-associated AFFs; estimates differed by race and cannot be generalized uncritically [32]. Prolonged exposure consequently warrants reassessment, especially after five years, rather than automatic cessation in every patient. Persistent thigh or groin pain should prompt clinical evaluation and appropriate imaging.

### 5.2. Medication-Related Osteonecrosis of the Jaw

Medication-related osteonecrosis of the jaw (MRONJ) is an uncommon but clinically important adverse event that requires consideration during long-term bisphosphonate treatment. Its occurrence is influenced by several factors, including the underlying disease, type and intensity of antiresorptive therapy, duration of exposure, and local oral health conditions. The risk is substantially greater in patients receiving high-dose antiresorptive regimens for malignant disease than in those treated for osteoporosis [33,34].

For patients receiving bisphosphonates at osteoporosis doses, the estimated incidence of MRONJ is low, although reported rates vary according to the population studied and the diagnostic criteria applied. Invasive dentoalveolar procedures, particularly tooth extraction, and pre-existing periodontal or dental infection are important clinical considerations. Nev-

ertheless, the occurrence of MRONJ cannot be attributed to dental procedures alone, and its pathogenesis is likely multifactorial.

These findings have practical implications for treatment planning. Assessment of oral health, management of active dental infection, and appropriate communication between the treating physician and dental professional may help reduce avoidable complications. In patients requiring invasive dental treatment, the decision to modify antiresorptive therapy should consider the individual fracture risk, cumulative treatment exposure, and complexity of the planned procedure. Importantly, evidence that a temporary interruption of bisphosphonate therapy reliably prevents MRONJ remains insufficient. Routine discontinuation solely before dental procedures is therefore not supported as a universal strategy [8,34].

From a clinical perspective, the possibility of MRONJ should prompt appropriate preventive measures and individualized assessment rather than automatic avoidance of bisphosphonates. For most patients with a substantial risk of osteoporotic fracture, the expected skeletal benefit remains considerably greater than the low absolute probability of this complication.

### 5.3. Adherence and Persistence

The effectiveness of oral bisphosphonate therapy in routine practice depends substantially on adherence. Real-world studies demonstrate that persistence with oral bisphosphonate treatment is frequently suboptimal [35–37]. A 2022 systematic review and network meta-analysis including 102 studies and more than 2.6 million participants found substantial differences in treatment persistence and compliance across bisphosphonate regimens [35]. The association between poor adherence and increased fracture incidence is supported separately by observational studies [36,37]. The distinction between efficacy and effectiveness is therefore particularly important for osteoporosis. A drug may demonstrate excellent efficacy in a randomized controlled trial while producing substantially less benefit in clinical practice if patients discontinue treatment or take it incorrectly. Alendronate requires specific administration conditions: it should be taken fasting with plain water, and the patient must remain upright after administration. Although weekly dosing improves convenience compared with daily treatment, these requirements may still limit persistence. Treatment selection should therefore incorporate not only pharmacological efficacy but also the probability that the patient will adhere to the prescribed regimen.

### 5.4. Bisphosphonates and Fall Prevention

Pharmacological treatment should be integrated with interventions addressing fall risk and physical function. Falls are a major proximal determinant of hip and other nonvertebral fractures, particularly among older adults [38]. Exercise programs incorporating balance and strength training can reduce fall risk, while resistance training may contribute to maintenance of muscle strength and BMD [39,40]. These interventions should complement rather than replace pharmacological therapy in patients who meet criteria for osteoporosis treatment. The clinical relevance is particularly strong in older patients with frailty, impaired balance, sarcopenia or previous falls.

### 5.5. Contemporary Treatment Sequencing

The role of bisphosphonates has evolved as therapeutic options have expanded. For many women at high fracture risk, oral alendronate, risedronate or intravenous zoledronate remain appropriate initial antiresorptive therapies [7–9]. However, patients with very high or imminent fracture risk represent a distinct clinical group. In such patients—particularly those with recent or multiple vertebral fractures, very low BMD or other markers of imminent fracture risk—rapid reduction in fracture probability may be prioritized. Osteoan-

abolic agents such as teriparatide, abaloparatide and romosozumab can produce more rapid and/or greater increases in BMD than conventional antiresorptive therapy in selected populations [18–21].

The Active-Controlled Fracture Study in Postmenopausal Women With Osteoporosis at High Risk (ARCH) trial provides particularly relevant evidence. In women at high fracture risk, one year of romosozumab followed by alendronate produced greater reductions in vertebral and clinical fracture outcomes than alendronate alone, although the cardiovascular safety signal associated with romosozumab requires careful patient selection [19].

These findings do not diminish the role of alendronate. Rather, they broaden it. Alendronate can serve as

- initial therapy for many women at high fracture risk;
- maintenance antiresorptive therapy after anabolic treatment;
- long-term therapy in patients with persistent high fracture risk;
- part of a sequential strategy after denosumab discontinuation.

The last role is particularly important. Denosumab does not accumulate in bone in the same manner as bisphosphonates. Its antiresorptive effect reverses relatively rapidly after treatment discontinuation, potentially resulting in a marked increase in bone turnover, rapid BMD loss and an increased risk of multiple vertebral fractures [41–43]. A planned bisphosphonate transition is therefore commonly incorporated into the management of patients discontinuing denosumab. Bisphosphonates consequently remain central to osteoporosis treatment even in an era increasingly characterized by sequential and goal-directed therapy.

## 6. Critical Appraisal of the Evidence

The evidence supporting bisphosphonates is substantial, but a critical interpretation requires explicit consideration of population selection, outcome-specific effect estimates, absolute benefit, certainty of evidence, long-term safety, adherence and treatment sequence.

a. The foundational evidence remains robust but is not universally applicable

The pivotal alendronate trials were methodologically strong, but their eligibility criteria and trial setting constrain direct generalization. FIT enrolled ambulatory postmenopausal women approximately 54–81 years of age with low femoral-neck BMD and excluded several groups commonly encountered in current practice, including women with significant renal or hepatic dysfunction, severe malabsorption, major recent or recurrent upper-gastrointestinal ulcer disease, unstable cardiovascular disease, selected endocrine disorders, and previous bisphosphonate exposure [15,16]. Trial participants also received protocolized follow-up and adherence support that are difficult to reproduce in routine care. Contemporary patients may be older, frailer and more likely to have multimorbidity, polypharmacy, falls, chronic kidney disease, cognitive impairment or competing mortality risks. Therefore, efficacy estimates from FIT remain foundational but should be translated into practice using current comorbidity, adherence and competing-risk profiles rather than applied as universal effect estimates.

b. Fracture endpoints are not interchangeable

Radiographic vertebral, clinical vertebral, nonvertebral and hip fractures are distinct endpoints, with different frequencies and precision. As consolidated in Table 1, FIT-1 demonstrates a substantial vertebral fracture benefit, whereas hip fracture estimates are less precise because fewer events occurred. FIT-2, which enrolled women without prevalent vertebral fractures, showed a significant reduction in radiographic vertebral fractures but not in overall clinical fractures [15,16]. Consequently, outcome-specific conclusions are more informative than a single generalized statement that alendronate prevents fractures.

c. Relative risk reduction should not be interpreted without absolute risk

FIT demonstrates why relative effects should be interpreted alongside absolute event rates, baseline fracture probability and the follow-up period (Table 1). For example, a substantial relative reduction in radiographic vertebral fractures in FIT-2 corresponded to a smaller absolute benefit than in the higher-risk FIT-1 population. Conversely, the FIT-2 subgroup with femoral-neck osteoporosis had a greater absolute reduction in clinical fractures than the overall FIT-2 cohort [15,16]. NNT values in Table 1 are therefore linked explicitly to their respective follow-up horizons and should not be compared as if they represented identical observation periods.

d. The 2025 Cochrane review appropriately introduces uncertainty

The 2025 Cochrane review confirms benefit but shows that certainty is outcome- and population-specific [24]. For secondary prevention, the review concluded that alendronate probably reduces clinical vertebral fractures, whereas evidence that it reduces nonvertebral, hip and wrist fractures was less certain ("may reduce"). For primary prevention, clinical vertebral and nonvertebral fracture reductions were also characterized with limited certainty, while hip and wrist fracture outcomes may show little or no difference. The review further judged evidence concerning withdrawals due to adverse events in higher-risk women to be very uncertain. These distinctions matter clinically: lower certainty for infrequent outcomes such as hip fracture does not prove absence of benefit, but it should temper overly precise claims and highlight the importance of baseline risk, event counts, confidence intervals and applicability to the individual patient.

e. Rare adverse events should be interpreted in absolute terms

The safety discussion should be interpreted alongside exposure duration and baseline fracture probability. AFF risk rises substantially with prolonged exposure, especially after approximately 3–5 years and progressively thereafter [32], whereas MRONJ remains very uncommon with osteoporosis-dose therapy [33]. These rare events therefore justify scheduled reassessment, symptom surveillance and individualized duration decisions rather than indiscriminate avoidance of bisphosphonates. In patients at persistently high fracture risk, the absolute number of typical fragility fractures prevented generally remains greater than the number of these rare treatment-associated events.

f. Modern osteoporosis therapy is increasingly goal-directed

The 2024 ASBMR/BHOF position statement emphasizes that treatment should be directed toward clinically meaningful fracture-prevention goals rather than simply toward prescribing a particular class of medication [10]. This approach requires consideration of

- previous fracture;
- fracture recency;
- fracture site and severity;
- hip and spine BMD;
- age;
- ongoing glucocorticoid exposure;
- falls and frailty;
- adherence;
- treatment history;
- expected treatment duration.

The implication is that two women with the same T-score may appropriately receive different treatments.

g. Bisphosphonates remain central, but not universal

Although bisphosphonates remain a cornerstone of osteoporosis management, their use should be guided by individual fracture risk rather than a uniform first-line approach. Patients at very high or imminent fracture risk may benefit from an anabolic-first strategy, followed by antiresorptive treatment, as outlined in Table 3.

**Table 3.** Contemporary role of bisphosphonates in the management of postmenopausal osteoporosis.

| Clinical Scenario | Preferred Treatment Strategy | Role of Bisphosphonates | Rationale |
|---|---|---|---|
| High fracture risk: osteoporosis-range BMD and/or fracture probability above the intervention threshold, without defining very-high-risk features [8,10,44]. | Antiresorptive therapy | First-line option | An oral bisphosphonate (alendronate or risedronate) or intravenous zoledronate is a standard option when suitable; select according to clinical risk, tolerability and preferences [8,44]. |
| Very high/imminent fracture risk: recent major fragility fracture (especially vertebral/hip), multiple vertebral fractures, very low BMD (e.g., T-score $\leq -3.5$ under NOGG), fracture on treatment, or a combination of major risk factors [8,10,44]. | Anabolic-first therapy, followed by antiresorptive treatment | Not necessarily first-line | Consider osteoanabolic-first therapy followed promptly by an antiresorptive agent in appropriately selected patients; definitions and treatment access vary between guidelines [8,10,19,22,44]. |
| After anabolic therapy | Sequential antiresorptive therapy | Consolidation therapy | Maintains and consolidates BMD and fracture-risk benefits achieved with anabolic treatment [10,18–22,44] |
| After denosumab discontinuation | Planned sequential antiresorptive therapy | Important transition option | Helps mitigate rebound bone loss and the associated risk of vertebral fractures [22,41,43] |
| Long-term management | Individualized, risk-stratified treatment | Central, but not universal | Treatment choice and sequence should reflect fracture risk, previous therapy and clinical context [8,10,22,23] |

BMD—Bone Mass Density; NOGG—National Osteoporosis Guideline Group.

## 7. Clinical Implications

These data support individualized treatment decisions rather than a fixed drug-duration rule. Initial treatment should be selected according to fracture probability and recency of fracture, with oral alendronate remaining appropriate for many high-risk women who can comply with administration requirements. Response and risk should be reassessed periodically; after approximately five years of oral therapy, consider continuation, alternative treatment or a monitored holiday according to current risk, not simply elapsed time [7,8,30]. Decision-making must incorporate uncertainty around individual fracture endpoints, cumulative exposure-related adverse events, renal and gastrointestinal suitability, and real-world adherence. Patients at very high or imminent risk may need an osteoanabolic-first sequence, followed by antiresorptive consolidation [8,10,19]. Functional assessment, fall prevention and appropriate exercise remain complementary strategies, not substitutes for indicated pharmacotherapy [38–40].

## 8. Limitations of This Review

This review has several limitations. First, as a structured narrative critical review, it relied on purposive rather than exhaustive selection of evidence; relevant studies may

therefore have been missed, and selection bias cannot be excluded. Second, no review protocol was registered, independent dual screening was not performed, and no formal study-level risk-of-bias assessment was undertaken, so judgements on certainty relied largely on published GRADE assessments. Third, the emphasis on alendronate limits conclusions about the comparative effectiveness of individual bisphosphonates, for which head-to-head trials are scarce. Fourth, the pivotal FIT and FLEX trials were conducted in selected populations several decades ago, and estimates of rare adverse events derive mainly from observational studies that are susceptible to residual confounding. Finally, guideline recommendations and definitions of very high or imminent fracture risk differ between regions and continue to evolve, so the treatment pathway presented here should be adapted to local guidance and treatment access.

## 9. Conclusions

Bisphosphonates continue to play a fundamental role in the treatment of postmenopausal osteoporosis, although their optimal use increasingly depends on individualized fracture-risk assessment and treatment sequencing. Alendronate has a well-established evidence base, with the most consistent antifracture effects demonstrated for vertebral fractures. Its benefit in preventing nonvertebral and hip fractures is also clinically relevant, particularly in women at higher baseline fracture risk, but the precision and certainty of these estimates vary across populations and outcomes [15–17,24].

The available evidence also highlights the importance of distinguishing treatment efficacy from long-term treatment strategy. The FLEX trial supports reassessment after approximately five years of oral alendronate rather than automatic continuation or discontinuation. Although residual skeletal effects may persist after withdrawal, treatment interruption is most appropriate for carefully selected patients whose current fracture risk permits a monitored drug holiday [30]. In contrast, women with previous major fragility fractures, very low BMD, or persistently high fracture probability may require continued antiresorptive treatment or an alternative therapeutic sequence.

Long-term safety should be considered within this individualized framework. The duration-dependent risk of atypical femoral fractures and the rare occurrence of medication-related osteonecrosis of the jaw warrant appropriate patient selection, surveillance, and periodic reassessment, but should not obscure the substantial fracture-prevention benefits of treatment in appropriately selected patients [31–33]. Equally important, suboptimal adherence may considerably reduce the effectiveness of oral bisphosphonates in routine clinical practice.

Contemporary osteoporosis management therefore requires a shift from a fixed, drug-centered approach toward risk-stratified and goal-directed care. Alendronate remains an appropriate initial option for many women at high fracture risk and an important antiresorptive component of sequential treatment. However, patients at very high or imminent fracture risk may benefit more from an osteoanabolic-first strategy followed by antiresorptive therapy [8,10,19,22,44]. The clinical value of alendronate lies not in its universal application, but in selecting the patients most likely to benefit, determining an appropriate treatment duration, and adapting therapy as fracture risk evolves.

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